Isomeric *N*,*N*-Bis(cyclohexanol)amine Aryl Esters: The Discovery of a New Class of Highly Potent P-Glycoprotein (Pgp)-dependent Multidrug Resistance (MDR) Inhibitors

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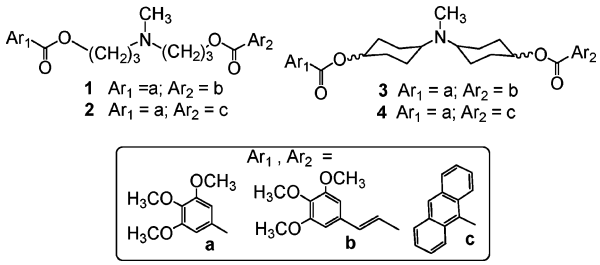
Abstract: A new series of P-glycoprotein (Pgp)-dependent multidrug resistance (MDR) inhibitors having a *N*,*N*-bis(cyclohexanol)amine scaffold have been designed, following the frozen analog approach. With respect to the parent flexible molecules, the new compounds show improved potency and efficacy. Among them, compound **1d**, on anthracycline-resistant erythroleukemia K562 cells, is able to completely reverse Pgp-dependent MDR at low nanomolar concentration.

Multidrug resistance (MDR) is a kind of acquired drug resistance of cancer cells and microorganisms to a variety of chemotherapic drugs that usually are structurally and mechanistically unrelated.[1] Multidrug resistance may originate from several biochemical mechanisms; classical MDR[2] is due to a lower cell concentration of cytotoxic drugs associated with accelerated efflux of the chemotherapeutic drug as a consequence of the overexpression of proteins such as ABCB1 (P-glycoprotein, Pgp) and ABCC1 (multidrug resistance associate protein 1, MRP1)[3] that act as extrusion pumps. These proteins belong to the ABC superfamily of transporters that use ATP as energy source, but several families of pumps that use a variety of energy sources are present in mammals and microorganisms.[1,4] In mammals, besides cancer cells, these proteins have been found in several important tissues and blood−tissue barriers where they apparently regulate the secretion of lipophilic molecules and the extrusion of xenobiotics that enter the organism.[5]

Direct information on the structure of Pgp and MRP1 is scarce,[6,7] but resolution of the structure of homologous bacterial transporters[8] has opened the way to the development of homology models[9,10] and provided many useful details on the structure of the recognition site of ABC transporters. According to these findings, the recognition sites appear to be large, flexible, and rich in amino acids able to establish a variety of interactions with substrates, in particular $\pi-\pi$, ion$-\pi$, hydrogen bond, and hydrophobic interactions.[11,12] All information collected so far points to the existence of a large, polymorphous drug recognition domain, where a variety of molecules can be accommodated in a plurality of binding modes.[13]

Inhibition of the functions of Pgp and sister proteins is considered a suitable approach to circumvent MDR and drugs possessing inhibitory properties have been and are actively being sought (reviewed by Teodori,[14] Avendano,[15] and Robert[16]), even if, so far, no drug has been approved for therapy.[17] Furthermore, a potential use of these agents may be to increase drug penetration to biologically important protective barriers, such as the blood−brain and blood−cerebrospinal fluid.[18] The main problems associated with the development of effective Pgp-mediated MDR inhibitors seem due to poor specificity, low potency, interference with physiological functions, and, as a consequence, interference with the pharmacokinetics of the chemotherapic used.

Chart 1. General Structures of Designed Compounds



Very recently, we have described a new family of MDR reverters, endowed with fairly good potency, designed on the basis of a new concept. In brief, given the properties of the Pgp recognition site described above, we guessed that flexible molecules carrying a basic nitrogen flanked, at suitable distances, by two (or three) aromatic moieties, would accommodate in the recognition cavity choosing the most productive binding modes and therefore would interact with high affinity with the protein. The good potencies of most of the compounds synthesized and studied confirmed our prediction that the entropy toll paid had been compensated by the enthalpy gain because flexible molecules can optimize their interaction within the recognition site.[19]

We are still building on this idea and further studies are in progress. At the same time, having in mind possible therapeutic applications, we decided to verify the consequences of a partial reduction of the very high flexibility of our compounds. In fact, it has empirically been shown that a high number of rotatable bonds is detrimental for good absorption and drug-likeness,[20,21] while it is well-known that flexibility does not favor selectivity. Toward this end, we designed a new series of molecules where the *N*,*N*-bis-arylalkylamine moiety of a previous series (**1**,[19] **2**) was substituted with *N*,*N*-bis-cyclohexylamine (**3**, **4**) (Chart 1). The aromatic moieties selected were those that gave the best results in the linear series. The scaffold chosen may give origin to four geometrical isomers of quite different shape that somehow represent restricted conformation analogs of the parent linear compounds **1** and **2**. According to the frozen analog approach,[22] they can provide further insight on the characteristics of the recognition site. In the present paper, we describe a set of such derivatives that are fairly potent inhibitors of Pgp-dependent MDR, reaching unprecedented low-nanomolar activity.

The reaction pathway used to synthesize the desired compounds (**3a**−**d** and **4a**−**d**) is presented in Scheme 1, and their chemical and physical characteristics are reported in Table S1 (Supporting Information).

The 4-oxocyclohexyl ester **5** was obtained by esterification of 4-hydroxycyclohexanone[23] with 3,4,5-trimethoxybenzoyl chloride. Compounds **6** were then obtained by reductive amination of compound **5** with *trans*-4-aminocyclohexanol or

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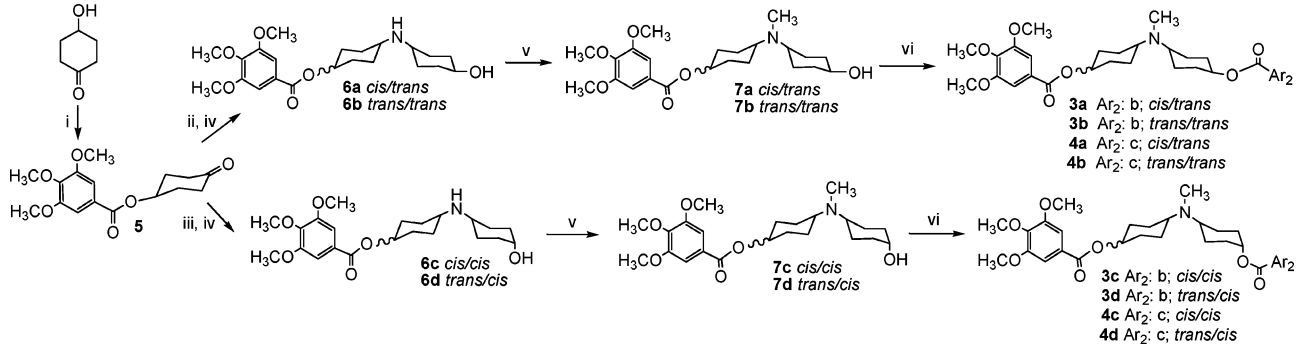
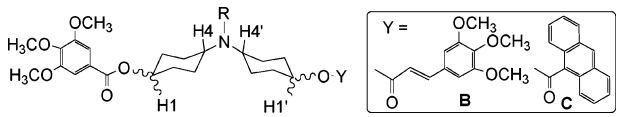
Scheme 1[a]



[a] Reagents and conditions: (i) $CHCl_3$, 3,4,5-trimethoxybenzoyl chloride; (ii) *trans*-4-aminocyclohexanol, $(^iPrO)_4Ti$, $NaBH_3CN$; (iii) *cis*-4-aminocyclohexanol, $(^iPrO)_4Ti$, $NaBH_3CN$; (iv) chromatographic separation; (v) HCOOH/HCHO; (vi) Ar_2COCl, $CHCl_3$. For the meaning of $Ar_1$and Ar_2, see Table 1.

Table 1. ^1H NMR Signals at 400 MHz



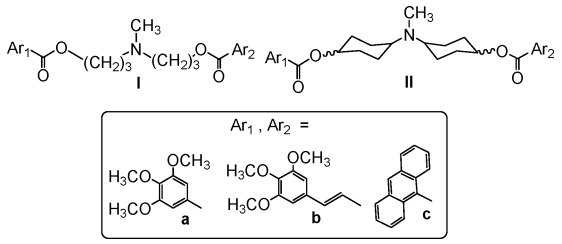
compd	R	Y	axial H1	equatorial H1	axial H1′	equatorial H1′	H4	H4′
6a	H	H		$\delta = 5.12^a$	$\delta = 3.60^a$		$\delta = 2.71^{a,c}$	$\delta = 2.59^{a,c}$
cis/trans				$w/2 = 15.6^b$	$J_{aa} = 10.6^b$		$J_{aa} = 9.6^b$	$J_{aa} = 10.8^b$
					$J_{ae} = 4.0^b$		$J_{ae} = 3.2^b$	$J_{ae} = 3.6^b$
6b	H	H	$\delta = 4.92^a$		$\delta = 3.62^a$		$\delta = 2.66^{a,c}$	$\delta = 2.60^{a,c}$
trans/trans			$J_{aa} = 10.8^b$		$J_{aa} = 10.6^b$		$J_{aa} = 11.2^b$	$J_{aa} = 10.8^b$
			$J_{ae} = 4.4^b$		$J_{ae} = 4.0^b$			
6c	H	H		$\delta = 5.15^a$		$\delta = 3.94^a$	$\delta = 2.81-2.70^{a,d}$	
cis/cis				$w/2 = 11.8^b$		$w/2 = 10.9^b$		
6d	H	H	$\delta = 4.93^a$			$\delta = 3.94^a$	$\delta = 2.80-2.72^{a,d}$	
trans/cis			$J_{aa} = 10.8^b$			$w/2 = 10.9^b$		
			$J_{ae} = 4.4^b$					
7a	CH_3	H		$\delta = 5.18^a$	$\delta = 3.61-3.51^a$		$\delta = 2.69-2.51^{a,d}$	
cis/trans				$w/2 = 13.3^b$	$w/2 = 26.7^b$			
7b	CH_3	H	$\delta = 4.95-4.78^a$		$\delta = 3.61-3.55^a$		$\delta = 2.70-2.50^{a,d}$	
trans/trans			$w/2 = 26.4^b$		$w/2 = 25.7^b$			
7c	CH_3	H		$\delta = 5.19^a$		$\delta = 3.96^a$	$\delta = 2.79-2.62^{a,d}$	
cis/cis				$w/2 = 12.1^b$		$w/2 = 10.9^b$		
7d	CH_3	H	$\delta = 4.93-4.81^a$			$\delta = 3.97^a$	$\delta = 2.77-2.56^{a,d}$	
trans/cis			$w/2 = 25.5^b$			$w/2 = 11.1^b$		
3a	CH_3	B		$\delta = 5.21^a$	$\delta = 4.80^a$		$\delta = 2.70-2.52^{a,d}$	
cis/trans				$w/2 = 10.2^b$	$J_{aa} = 10.2^b$			
					$J_{ae} = 4.4^b$			
3b	CH_3	B	$\delta = 4.92^a$		$\delta = 4.80^a$		$\delta = 2.75-2.52^{a,d}$	
trans/trans			$J_{aa} = 9.2^b$		$J_{aa} = 10.2^b$			
			$J_{ae} = 4.4^b$		$J_{ae} = 4.4^b$			
3c	CH_3	B		$\delta = 5.22^a$		$\delta = 5.11^a$	$\delta = 2.85-2.58^{a,d}$	
cis/cis				$w/2 = 9.1^b$		$w/2 = 10.7^b$		
3d	CH_3	B	$\delta = 4.95-4.85^a$			$\delta = 5.11^a$	$\delta = 2.88-2.58^{a,d}$	
trans/cis			$w/2 = 21.6^b$			$w/2 = 9.6^b$		
4a	CH_3	C		$\delta = 5.18^a$	$\delta = 5.38-5.26^a$		$\delta = 2.76-2.55^{a,d}$	
cis/trans				$w/2 = 11.2^b$	$w/2 = 24.1^b$			
4b	CH_3	C	$\delta = 4.92^a$		$\delta = 5.38-5.25^a$		$\delta = 2.75-2.68^{a,d}$	
trans/trans			$J_{aa} = 10.4^b$		$w/2 = 26.4^b$			
			$J_{ae} = 4.4^b$					
4c	CH_3	C		$\delta = 5.17^a$		$\delta = 5.60^a$	$\delta = 2.76-2.58^{a,d}$	
cis/cis				$w/2 = 10.8^b$		$w/2 = 9.1^b$		
4d	CH_3	C	$\delta = 4.91-4.82^a$			$\delta = 5.60^a$	$\delta = 2.76-2.58^{a,d}$	
trans/cis			$w/2 = 25.4^b$			$w/2 = 11.4^b$		

[a] Parts per million. [b] Hertz. [c] The attribution of H4 and H4′ signal can be interchanged. [d] Superimposed signals.

cis-4-aminocyclohexanol,[24] using titanium(IV) isopropoxide as Lewis acid catalyst and $NaBH_3CN$ as reducing agent, according to the Mattson procedure.[25] The secondary amines obtained are an approximately 1:1 mixture of *cis*/*trans* and *trans*/*trans* isomers or *cis*/*cis* and *trans*/*cis* isomers, respectively, as results from ^1H NMR spectra.

A chromatographic separation was performed on the amines **6**, and the pure isomers **6a**, **6b**, **6c**, and **6d** were obtained. Their configuration was attributed on the basis of the ^1H NMR characteristics of the cyclohexane protons at C1, C4 and C1′, C4′ (Table 1). In most cases, it was possible to extract the J_{aa} and sometimes the J_{ae} constants; when the signal does not allow extraction of the coupling constants, the half-height amplitude of the signal ($w/2$)[26−28] allows confident attribution of their equatorial or axial nature. Moreover the chemical shift of the signal is diagnostic, because axial protons resonate at higher

Table 2. MDR-Reverting Activity of Compounds **3a**−**d** and **4a**−**d**



compd	structure	Ar_1	Ar_2	$[I]_{0.5}$ (μM)[a]	α_{max}[b]
3a *cis*/*trans*	II	a	b	0.09 ± 0.015	0.85
3b *trans*/*trans*	II	a	b	0.32 ± 0.10	0.81
3c *cis*/*cis*	II	a	b	0.03 ± 0.01	0.80
3d *trans*/*cis*	II	a	b	0.01 ± 0.001	0.98
4a *cis*/*trans*	II	a	c	0.30 ± 0.06	0.95
4b *trans*/*trans*	II	a	c	0.30 ± 0.06	0.88
4c *cis*/*cis*	II	a	c	0.18 ± 0.03	0.79
4d *trans*/*cis*	II	a	c	0.16 ± 0.04	0.78
1	I	a	b	0.60 ± 0.15[c]	0.90
2	I	a	c	0.28 ± 0.05	0.71
verapamil				1.60 ± 0.03	0.70
MM36				0.05 ± 0.01[d]	0.70

[a] Concentration of the inhibitor that causes a 50% increase in nuclear concentration of pirarubicin ($\alpha = 0.5$). [b] Efficacy of MDR modulator and maximum increase that can be obtained in the nuclear concentration of pirarubicin in resistant cells. [c] See ref 19. [d] See ref 30.

fields, while the corresponding equatorial ones are deshielded.

The isomers **6a** and **6c** present the C1 proton with equatorial characteristics ($\delta = 5.12$ ppm, $w/2 = 15.6$ Hz and $\delta = 5.15$ ppm, $w/2 = 11.8$ Hz, respectively), while isomers **6b** and **6d** present the C1 proton with axial characteristics ($\delta = 4.92$ ppm, $J_{aa} = 10.8$ Hz, $J_{ae} = 4.4$ Hz and $\delta = 4.93$ ppm, $J_{aa} = 10.8$ Hz, $J_{ae} = 4.4$ Hz respectively). The isomers **6a** and **6b** present the C1′ proton with axial characteristics ($\delta = 3.60$ ppm, $J_{aa} = 10.6$ Hz, $J_{ae} = 4.0$ Hz and $\delta = 3.62$ ppm, $J_{aa} = 10.6$ Hz, $J_{ae} = 4.0$ Hz, respectively), while isomers **6c** and **6d** present the C1′ proton with equatorial characteristics ($\delta = 3.94$ ppm, $w/2 = 10.9$ Hz for both isomers). Furthermore, the protons of the two carbon atoms carrying the amine function have axial characteristics in every isomer of **6** (see Table 1); this indicates that the two cyclohexane rings are in *cis*/*trans* (**6a**), *trans*/*trans* (**6b**), *cis*/*cis* (**6c**), and *trans*/*cis* (**6d**) configurations. Therefore, ^{1}H NMR data show that **6a** and **6c** are frozen in a conformation having the bulky susbstituent in position 1 forced into an axial position, while **6b** and **6d** have the same group in the more relaxed equatorial position as shown in Table 1.

Reductive methylation of **6a**−**6d** with HCOOH/HCHO gave the corresponding tertiary amines **7a**−**7d**. Final compounds **3a**−**d** and **4a**−**d** were then obtained by reaction of **7a**−**d** with the proper acyl chloride. The ^{1}H NMR data reported in Table 1 show that the configurations of **6a**−**d** are maintained in compounds **7a**−**d** and then in the final products **3a**−**d** and **4a**−**d**, ruling out any isomerization in the subsequent reactions. Compound **2** (Chart 1) was synthesized for comparative purposes by reaction of anthracene-9-carboxylic acid 3-(3-hydroxypropyl-methylamino)propyl ester[19] with 3,4,5-trimethoxybenzoic acid using 1-(3-dimethylamino-propyl)-3-ethylcarbodimmide hydrochloride (EDAC) as the coupling reagent (see Supporting Information).

The information obtained from ^{1}H NMR on preferred conformations was confirmed by molecular modeling (Figure S1, see Supporting Information) where compounds **3a**−**d** are shown in their lowest energy conformation with the 3,4,5-trimethoxybenzoate group in axial position. The lowest energy conformations of the set of isomers **4** are practically identical.

The ability of compounds **3a**−**d** and **4a**−**d** to revert MDR was evaluated on anthracycline-resistant erythroleukemia K562 cells, measuring the uptake of pirarubicin by continuous spectrofluorometric signal of the anthracycline at 590 nm ($\lambda_{ex} = 480$ nm) after incubation of the cells, following previously reported protocols.[27,29,30] MDR-reverting activity is described by (i) α, which represents the fold increase in the nuclear concentration of pirarubicin in the presence of the MDR-reverting agent and varies between 0 (in the absence of the inhibitor) and 1 (when the amount of pirarubicin in resistant cells is the same as in sensitive cells); (ii) α_{max}, which expresses the efficacy of the MDR-modulator and is the maximum increase that can be obtained in the nuclear concentration of pirarubicin in resistant cells with a given inhibitor; and (iii) $[I]_{0.5}$, which measures the potency of the MDR-reverting agent and represents the concentration of the inhibitor that causes a half-maximal increase ($\alpha = 0.5$) in nuclear concentration of pirarubicin (see Table 2). Even if binding data on Pgp are not available at the moment, this test indicates that active compounds inhibit the Pgp-operated extrusion of the reporter molecule pirarubicin, as does the reference molecule verapamil. The molecules studied in this work did not show any detectable antiproliferative activity at the doses used in the test.

The results obtained on anthracycline-resistant erythroleukemia K562 cells are reported in Table 2, together with those of the parent linear compounds **1**[19] and **2** (Chart 1) and of MM36[30] and verapamil used as reference compounds.

The new molecules are all potent and efficacious inhibitors of MDR and, in general, present improved potency and efficacy with respect to the parent flexible compounds. However, some interesting differences can be observed between the two sets of isomers. The four isomers of **3** are all more potent than the flexible parent compound **1**. As far as isomers **4** are concerned, the improvement with respect to the flexible compound **2** is less impressive and, actually, regards only two isomers. However, the trend of potencies is very much the same in the two sets, where the isomers with *cis*/*cis* and *trans*/*cis* configuration are the most potent, indicating that such configurations allow optimal binding to the recognition site. Apparently, as the conformational freedom is reduced, the nature of the aromatic moieties gains importance, a consequence that is in accord with our original hypothesis that flexible molecules can more easily find the most productive interaction with the recognition site. As a matter of fact, the anthracene moiety (set **4**), which produced very effective Pgp inhibitors in flexible molecules (see compound **2**, but also the analogous compounds reported in the previous exploratory work[19]), appears to be less effective than the *trans*-3,4,5-trimethoxycinnamic one (set **3**) in rigidified structures.

Therefore, modulation of molecular flexibility and a careful choice of the aromatic moieties can give compounds possessing very interesting Pgp inhibitory properties. As a matter of fact, compound **3d**, which shows low nanomolar potency ($[I]_{0.5} = 0.01$ μM) and is able to completely reverse Pgp-dependent MDR ($\alpha = 0.98$) in anthracycline-resistant erythroleukemia K562 cells, is a very interesting compound that deserves further

investigation and can be a very useful lead for the development of clinically useful MDR modulators.

Supporting Information Available: Lowest energy conformations of **3a**−**3d** (Figure S1); experimental details for the synthesis of the reported compounds; and chemical and physical characteristics (Table S1), IR and ^{1}H NMR spectra (Table S2), and elemental analyses (Table S3) of compounds **2**, **3a**−**d**, and **4a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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